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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,194	10/15/2001	Avi J. Ashkenazi	GNE.2630P1C10	5226

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/978,194	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *please see attached sheets*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *58-65,68-70*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

ATTACHMENT TO ADVISORY ACTION

Claims 58-65 and 68-70 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 58-65 and 68-70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis of these rejections is of record.

Applicant's arguments (submitted in the after-final response of 15 July 2004) have been fully considered but are not found to be persuasive for the following reasons. The Polakis declaration under 37 CFR 1.132 filed 15 July 2004 is insufficient to overcome the rejection of claims 58-65 and 68-70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching that there is a general trend but no strong correlation between protein expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast proteins. Applicant further characterizes Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and protein for most of the 80 yeast proteins studied, but the correlation is not linear and thus one cannot accurately predict protein levels from

mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and protein. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and protein levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO351. There is no evidence regarding whether or not the PRO351 **mRNA** or **protein** levels are also increased in these tumor samples. Since the instant claims are directed to PRO351 **protein**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and protein levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka et al. was cited as evidence showing lack of correlation between gene amplification and increased protein levels. Haynes et al. was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO351 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or protein levels. One skilled in the art would do further research to determine whether or not the PRO351 protein levels

increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded protein. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Orntoft et al.

appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO351 in the instant specification. That is, it is not clear whether or not PRO351 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed proteins. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate protein levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form.

Accordingly, the specification's assertions that the claimed PRO351 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO351 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 58-65 and 68-70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the examiner can independently draw

conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

For all of these reasons, the rejections are maintained.

Conclusion

No claims are allowed.

Upon review of the application, it was noted that the Haynes et al., Konopka et al., and Pennica et al. references were not scanned into the electronic file wrapper. In

case the Applicant's records are also incomplete, enclosed is a PTO-892 form and copies of the three references in question.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER